Lipoproteins and diabetes

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Ever since the French—German pathologist Jean Lobstein coined the term arteriosclerosis in 1833, the disease has been intensively investigated. In 1793, Edward Jenner, later a celebrity for his contribution to smallpox vaccination, performed an autopsy on his colleague John Hutner who had died suddenly during a heated discussion at a board meeting at St. George’s Hospital in London. In his notes he wrote: ‘I found no material disease of the heart, except that the coronary arteries were thickened’. Rudolf Virchow was the first to recognize the inflammatory nature of atherosclerosis and the role of lipids therein, a concept that is still stands true today. It was a Russian military physician, however, who—behind the Iron Curtain in 1913—proved the concept by feeding rabbits with a high-fat diet. With his experiment, Nikolai N. Anichkov showed that lipid-rich plaques had developed under these circumstances in the aorta of the animals. Once the Framingham study confirmed the importance of high cholesterol for the development of myocardial infarction, stroke, and death in US and European populations, cholesterol became a therapeutic target. Thanks to the discovery of Akiro Endo, statins, together with antihypertensive drugs and aspirin, became a cornerstone in cardiovascular prevention and contributed to the rise of cardiovascular medicine. Today, LDL cholesterol (LDL-C) and statins are used extensively in clinical practice and are part of several guidelines of the European Society of Cardiology in individuals at risk and patients with established coronary artery disease.

The current issue of the European Heart Journal focuses on lipoproteins and diabetes. In spite of all the progress made, several aspects of lipids in cardiovascular disease remain unresolved, in particular the management of homozygous autosomal dominant hypercholesterolemia, the role of HDL cholesterol (HDL-C), and obesity. Novel treatment strategies beyond statins have been developed for severe elevated LDL-C, while several attempts to modify HDL-C pharmacologically have failed.

In the first paper, entitled ‘Mendelian randomization of blood lipids for coronary heart disease’, Michael Holmes from the University of Pennsylvania in Philadelphia, USA reports on a different approach. He investigated the causal role of HDL-C and triglycerides in coronary heart disease using multiple instrumental variables for Mendelian randomization, a powerful method using variation in genes of known function to examine possible causal effects increasingly used in epidemiological studies. Both the unrestricted and restricted allele scores they developed for LDL-C were associated with coronary artery disease. For HDL-C, the unrestricted allele score was associated with coronary artery disease, per 1 mmol/L higher HDL-C, but neither the restricted allele score nor the unrestricted HDL-C allele score adjusted for triglycerides, LDL-C, or statin use showed this association. In contrast, for triglycerides, the unrestricted allele score and the restricted allele score were both associated with coronary artery disease per 1 log unit increment. However, the unrestricted triglyceride score adjusted for HDL-C, LDL-C, and statin use gave an odds ratio for coronary artery disease of only 1.01. The authors therefore conclude that genetic findings support a causal effect of triglycerides on coronary risk, but a causal role for HDL-C, though possible, remains less certain—a finding that seems to be in line with the disappointing results of recent pharmacological trials aimed at increasing HDL-C to prevent future cardiovascular events.

In the second paper, ‘Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study’ by Guy-Marino Hinnouho from INSERM U1018, Villejuif, France, the authors evaluated the role of obesity in cardiovascular risk. The metabolically healthy obese are individuals who, while overweight, have a favourable metabolic profile. Their outcome remains uncertain and thus worth investigating. In 7122 participants of the Whitehall II study, body mass index and the metabolic profile were assessed using the Adult Treatment Panel-III criteria. Incident coronary heart disease or stroke as well as type 2 diabetes were documented. A total of 657 individuals (9.2%) were obese, and 42.5% of these were classified as metabolically healthy. During 17 years of follow-up, 828 cardiovascular events occurred and 798 participants developed type 2 diabetes. Compared with metabolically healthy, normal weight individuals, metabolically healthy obese subjects had an almost doubled risk of cardiovascular disease and a three-fold risk of developing type 2 diabetes. As expected, for type 2 diabetes there was a doubling of risk in the metabolically unhealthy obese compared with their metabolically healthy counterparts, but not for cardiovascular events. It appears that the risk of the metabolically healthy obese for type 2 diabetes is lower than that of the metabolically unhealthy obese, but for cardiovascular disease the risk is equally elevated in both obesity phenotypes.

In the third paper, entitled ‘Homozygous autosomal dominant hypercholesterolaemia in The Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome’, John J.P. Kastelein from the Academic Medical Center in Amsterdam in The Netherlands studied homozygous autosomal dominant hypercholesterolaemia, an orphan disease caused by mutations in LDL-receptor, the apolipoprotein B100, or proprotein convertase subtilisin/kexin type 9 (PCSK9). All these mutations lead to elevated...
plasma LDL-C levels and a high risk for premature cardiovascular disease. The exact prevalence of molecularly defined homozygous autosomal dominant hypercholesterolaemia is unknown. Therefore, the authors investigated the prevalence and phenotypical characteristics of this disease in The Netherlands. Out of 104 682 individuals screened for molecular defects, 49 were classified as homozygous autosomal dominant hypercholesterolaemia, i.e. 0.05%. Twenty individuals were true homozygotes and 25 were compound heterozygotes for LDL-receptor mutations, and four were homozygous for apolipoprotein B100 mutations. Surprisingly, no bi-allelic PCSK9 mutation carriers were identified. Consequently, the prevalence of homozygous autosomal dominant hypercholesterolaemia was estimated to be ～1:300 000. The authors concluded that the prevalence of molecularly defined homozygous autosomal dominant hypercholesterolaemia is much higher and the clinical phenotype is more variable than assumed. As novel therapies such as mipomersen or PCSK9 inhibitors are or will be registered shortly for the treatment of such patients, a uniform definition as either a phenotypic or a molecular entity appears useful to determine which patients might be eligible for such novel agents.

The fourth manuscript, Long-term efficacy and safety of mipomersen in patients with familial hypercholesterolaemia: 2-year interim results of an open-label extension, authored by Raul Santos of the Heart Institute InCor of the University of Sao Paulo, Brazil, further evaluated novel treatment options. Mipomersen is an antisense therapeutic that targets the mRNA for apolipoprotein B100 and has to be administered subcutaneously as 200 mg weekly injections on top of maximally tolerated lipid-lowering therapy. In the present study, 130 patients with familial hypercholesterolaemia were enrolled. The mean decreases in LDL-C plasma levels from baseline to weeks 26, 52, 76, and 104 were 28, 27, 27, and 28%, respectively. For apolipoprotein B100, the corresponding values were 29, 28, 30, and 31%, respectively. Reductions in total cholesterol, non-HDL-C, and lipoprotein(a) were comparable with those of LDL-C. HDL-C increased from baseline by 6–7%. The long-term safety profile of mipomersen was excellent. Adverse events included injection site reactions and flu-like symptoms. There was an incremental increase in the median liver fat during the initial 6–12 months that appeared to diminish with continued mipomersen exposure beyond 1 year and returned toward baseline after the last drug dose, suggestive of adaptation. The median alanine aminotransferase level showed a similar trend over time. The authors concluded that long-term treatment with mipomersen for up to 2 years provides sustained reductions in all atherogenic lipoproteins and that the safety profile is acceptable and in line with previous controlled trials in these high-risk patient populations.

The current issue is complemented by a provocative Current Opinion by Franz Messerli from the St. Luke’s-Roosevelt Hospital Center and Columbia University, New York, USA entitled Wilder’s principle: pre-treatment evaluation post-treatment response. The phenomenon whereby the pre-treatment level of vital parameters, for instance of blood pressure, determines to a large extent the change per se, i.e. the principle of initial value (German: Ausgangswertgesetz) was first described by Josef Wilder in 1931 who proposed that the ‘direction of response of body function to any agent depends to a large degree on the initial value of that function’. This law applies for many other conditions, and hence its recognition appears important both for physicians and for clinical researchers alike, as outlined by the author. The editors sincerely hope that this valuable issue of the European Heart Journal captures the interest of its readers.

References


